UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO
09/487,851	01/19/2000	Robert J. Levy	7600-20U1 (CHOP-0013)	3653

7590 07/29/2002

Foley & Lardner
3000 K Street, N.W. Suite 500
Washington Harbour
Washington, DC 20007-5109

EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	22

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/487,851	Applicant(s) LEVY ET AL.	
	Examiner Janice Li	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)[·] Responsive to communication(s) filed on *05 March 2002* .

2a)[·] This action is **FINAL**. 2b)[ ] This action is non-final.

3)[ ] Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)[·] Claim(s) *1-38 and 65-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)[ ] Claim(s) _____ is/are allowed.

6)[·] Claim(s) *1-38 and 65-68* is/are rejected.

7)[ ] Claim(s) _____ is/are objected to.

8)[ ] Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)[ ] The specification is objected to by the Examiner.

10)[ ] The drawing(s) filed on _____ is/are: a)[ ] accepted or b)[ ] objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)[ ] The proposed drawing correction filed on _____ is: a)[ ] approved b)[ ] disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)[ ] Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)[ ] All b)[ ] Some * c)[ ] None of:

1.[ ] Certified copies of the priority documents have been received.

2.[ ] Certified copies of the priority documents have been received in Application No. _____ .

3.[ ] Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) [ ] The translation of the foreign language provisional application has been received.

15)[ ] Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) [x] Notice of References Cited (PTO-892)
2) [ ] Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) [ ] Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) [ ] Interview Summary (PTO-413) Paper No(s). _____ .
5) [ ] Notice of Informal Patent Application (PTO-152)
6) [x] Other: *detailed action* .

DETAILED ACTION

This action is a response to the Response under 37 CFR 1.111 (Paper #16) and Request for continuance of Prosecution and the Supplemental response (Paper # 21) filed on August 2001 and March 2002, respectively.

Claims 1-38 and 65-68 are pending in the present application and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-38 and 65-68 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In Paper #16, applicants assert that the Examiner has not provided a tenable basis for rejecting the claims of the instant application, that the claimed invention described methods that are novel and useful in instances where gene therapy works, the unpredictability of gene therapy is therefore irrelevant; applicants recite several titles of newspaper articles (Johannes and Henderson) without supplying or detailed discussion of the articles as the support for the enablement disclosure regarding gene therapy; applicants further argue that working examples should not be the touchstone

for the enabling quality of their specification, that the first paragraph of Section 112 does not require an applicant to demonstrate that each of the species within the genus in the claimed invention works, that it is the Examiner's burden to show that delivery HERG will not achieve a therapeutic effect.

The arguments have been carefully considered, but found NOT persuasive for the reasons of record advanced in Papers #7 and #11, and the following.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention in the instant case and the conclusion that the instant specification fails to provide an enabling disclosure for those skilled in the art intending to practice the invention is based on the combined evaluation of *Wands* factor, i.e. the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). M.P.E.P. teaches, "THE TEST OF ENABLEMENT IS WHETHER ONE REASONABLY SKILLED IN THE ART COULD MAKE OR USE THE INVENTION FROM THE DISCLOSURES IN THE PATENT COUPLED WITH INFORMATION KNOWN IN THE ART WITHOUT UNDUE EXPERIMENTATION." (UNITED STATES V. TELECTRONICS, INC., 857 F.2D 778, 785, 8 USPQ2D 1217, 1223 (FED. CIR. 1988)). "DETERMINING ENABLEMENT IS A QUESTION OF LAW BASED ON UNDERLYING FACTUAL FINDINGS". IN RE VAECK, 947 F.2D 488, 495, 20 USPQ2D 1438, 1444 (FED. CIR.1991); ATLAS POWDER CO. V. E.I. DU PONT DE NEMOURS & CO., 750 F.2D 1569, 1576, 224 USPQ 409, 413 (FED. CIR. 1984). One aspect of such factual evidence to be considered is "IF LITTLE IS KNOWN IN THE PRIOR ART ABOUT THE NATURE OF THE INVENTION AND THE ART IS UNPREDICTABLE, THE SPECIFICATION WOULD NEED MORE DETAIL AS TO

HOW TO MAKE AND USE THE INVENTION IN ORDER TO BE ENABLING. THE "PREDICTABILITY OR LACK THEREOF" IN THE ART REFERS TO THE ABILITY OF ONE SKILLED IN THE ART TO EXTRAPOLATE THE DISCLOSED OR KNOWN RESULTS TO THE CLAIMED INVENTION. IF ONE SKILLED IN THE ART CAN READILY ANTICIPATE THE EFFECT OF A CHANGE WITHIN THE SUBJECT MATTER TO WHICH THE CLAIMED INVENTION PERTAINS, THEN THERE IS PREDICTABILITY IN THE ART. ON THE OTHER HAND, IF ONE SKILLED IN THE ART CANNOT READILY ANTICIPATE THE EFFECT OF A CHANGE WITHIN THE SUBJECT MATTER TO WHICH THAT CLAIMED INVENTION PERTAINS, THEN THERE IS LACK OF PREDICTABILITY IN THE ART. ACCORDINGLY, WHAT IS KNOWN IN THE ART PROVIDES EVIDENCE AS TO THE QUESTION OF PREDICTABILITY. IN PARTICULAR, THE COURT IN IN RE MARZOCCHI, 439 F.2D 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), STATED: [I]N THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES WHEN THE WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE A REASONABLE DOUBT AS TO THE ACCURACY OF A PARTICULAR BROAD STATEMENT PUT FORWARD AS ENABLING SUPPORT FOR A CLAIM. THIS WILL ESPECIALLY BE THE CASE WHERE THE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES. MOST OFTEN, ADDITIONAL FACTORS, SUCH AS THE TEACHINGS IN PERTINENT REFERENCES, WILL BE AVAILABLE TO SUBSTANTIATE ANY DOUBTS THAT THE ASSERTED SCOPE OF OBJECTIVE ENABLEMENT IS IN FACT COMMENSURATE WITH THE SCOPE OF PROTECTION SOUGHT AND TO SUPPORT ANY DEMANDS BASED THEREON FOR PROOF. [FOOTNOTE OMITTED.] (MPEP 2164.02, 03)

Because the specification does not provide a disclosure that has reduced to practice to *any one* species of the genus for the methods of reverse gene therapy, each and every element of aforementioned *Wands* factors are carefully evaluated in the previous Office actions.

The Office actions Papers #7 and #11 not only illustrated that the general state of the art of gene therapy is underdeveloped and unpredictable citing references ranging from before to after the effective filing date of the instant application, such as *Eck et al, Orkin et al, and Boucher et al,* but also provide evidence to indicate that several species of the claimed genus, which are genes contemplated in the claims and the specification, do not work as expected or claimed, such as the p53 gene taught by *Vinyals et al* and Cre-mediated FasL system taught by *Okuyama et al.* The Office further cited teachings of *Sanguinetti and Kagan et al* to specifically address the exemplary gene "HERG" to indicate why the effect of mutant HERG on the dog model of re-entrant atrial flutter is not predictable until the actual effect is shown. The Office relied on the combined teachings of the prior- and post-filing date art to provide a reasonable basis to show that one skill in the art could not practice the invention without undue experimentation. "WHEN CONSIDERING THE FACTORS RELATING TO A DETERMINATION OF NON-ENABLEMENT, IF ALL THE OTHER FACTORS POINT TOWARD ENABLEMENT, THEN THE ABSENCE OF WORKING EXAMPLES WILL NOT BY ITSELF RENDER THE INVENTION NON-ENABLED." "LACK OF A WORKING EXAMPLE, HOWEVER, IS A FACTOR TO BE CONSIDERED, ESPECIALLY IN A CASE INVOLVING AN UNPREDICTABLE AND UNDEVELOPED ART." (MPEP 2164.02, 03) Therefore, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Citing general articles to support a novel approach does not provide sufficient support to enable the instant specification; the general knowledge and

levels of skill in the art do not supplement the omitted guidance, because specific, not general guidance is what is needed. Therefore, it is in error for applicant to request that the Examiner show particularly that delivery HERG will not achieve a therapeutic effect, to the contrary, it is applicants duty to disclose each aspect of the invention in such a way as MPEP indicated, "THE DISCLOSURE CORRESPONDING TO EACH ASPECT OF THE INVENTION MUST BE ENABLING TO A PERSON SKILLED IN EACH RESPECTIVE ART. (MPEP 2106.B.2)

In the supplemental Response, applicants submitted additional data, demonstrating expression and membrane-localization of both the wide-type and mutant channels in HEK293 cells and stem cells *in vitro*, that the mutant Q9E MiRP channel has influenced biophysical function of the K+ channel in normal cells *in vitro*, and that 15% of cardiac myocytes were transfected in pig right atrial samples *in vivo*. These additional data, however, has not provide sufficient enabling disclosure for the scope of the claims because the biophysical influence of the mutant gene has not been shown *in vivo* or in cells with abnormal K^+ channel, and has not translated to any therapeutic benefit in alleviating any disease or disorder in any affected animal as instantly claimed. It remains to be the position of the Office that the *in vitro* and *in vivo* data are not well correlated in gene therapy art as taught by *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) for example, which has been cited in the previous Office action and will be reiterated here, "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CF LUNG DISEASE IS IMMINENT. THE INABILITY TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY

MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD." Applicants are reminded of numerous factors complicating gene therapy, which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. These factors include the fate of the DNA vector itself (volume of distribution, rate of clearance, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the host immune response etc.), the *in vivo* consequences of altered gene expression and protein function, the stability of the mRNA produced, the amount and stability of the protein produced, the compartmentalization and secretory fate of the protein within the cell. These factors differ dramatically based on the vector used, the protein being produced, the organs and tissues involved and the disease being treated. (*Eck et al*, pg81, col 2, paragraph 3, and page 82, col. 1, paragraph 2). The unpredictability of gene therapy is also caused by the lack of knowledge in understanding the etiology and mechanism of a disease. For example, *Alton et al* (Lancet 1999 Mar; 353:947-54) teach after successful attempt to partially correct chloride channel biophysical activity *in vivo*, "WE WERE UNABLE TO SHOW ANY CORRECTION OF THE INCREASED SODIUM ABSORPTION", "AT PRESENT, IT IS NOT CLEAR WHETHER BOTH SODIUM AND CHLORIDE ABNORMALITIES NEED TO BE CORRECTED FOR CLINICAL BENEFIT; NOR IS IT CLEAR WHETHER ONLY THE LATTER REQUIRES CORRECTION, AND TO WHAT DEGREE IT NEEDS TO BE RESTORED TO PREVENT OR TREAT THE LUNG DISEASE", "IF THE SODIUM ABNORMALITY ALSO REQUIRES CORRECTION FOR CLINICAL BENEFIT, GENE THERAPY FOR CYSTIC FIBROSIS IS SOME WAY SHORT OF SUCH A TARGET".

In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means

for executing reverse gene therapy which awaits further development to the practical level.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* and *ex vivo* reverse gene therapy, in particular for alleviating any disease or disorder in any affected animal including human, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to *in vivo* and *ex vivo* gene therapy of any and all diseases or disorders, and the breadth of the claims directed to the use of numerous therapeutic genes/promoters combinations, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

For the reasons of record and those set forth above, the instant specification fails to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The prior rejection of claims 1-38 and 65-68 under 35 U.S.C. 112, second paragraph is withdrawn in view of the argument.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-

1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
July 23, 2002

JAMES KETTER
PRIMARY EXAMINER